CNS Involvement in Hemophagocytic Lymphohistiocytosis: CT and MR Findings

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Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder that is characterized by proliferation of benign histiocytes, and this commonly involves the liver, spleen, lymph nodes, bone marrow and central nervous system (CNS). We report here on the CT and MR imaging findings in a case of CNS HLH that showed multiple ring enhancing masses mimicking abscess or another mass on the CT and MR imaging.

Index terms:
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Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder that is characterized by nonmalignant diffuse infiltration of multiple organs, including the central nervous system (CNS), by lymphocytes and histiocytes (1). Many radiologic reports describing diffuse white matter infiltrations, parenchymal atrophy and calcification have been published, but the characteristics of these findings remain non-specific, especially in immunocompromised patients. We present here a case of HLH in a 3-year-old boy who presented with multiple ring enhancing lesions involving the brain.

CASE REPORT

A 3-year-old boy was admitted to the emergency unit with seizures and fever (38.3°). He had a history of virus-associated hemophagocytic syndrome that was diagnosed by bone marrow biopsy four months earlier, and the patient had received immunosuppressive chemotherapy in accordance with the HLH-94 protocol. On admission, the laboratory data revealed leukopenia (3,600 WBC/mm^2) and a normal range of the erythrocyte sedimentation rate (ESR) (10 mm/hr), C-reactive protein (CRP) (< 0.2 mmg/dl), and the hematocret (33.6%). The examination of the cerebrospinal fluid (CSF) revealed an elevated protein level (136 mg/dL), a normal glucose level (75 mg/dL) and 11 WBC/mm^3. The bone marrow biopsy showed no evidence of abnormal cell clusters.

The brain CT showed multiple irregular, thick walled, ring enhancing nodules in the both cerebral hemispheres and the right cerebellum. These lesions were scattered mainly at the white-gray matter junction, and the examination showed marked perilesional edema with a mass effect to the adjacent ventricle. Some of these lesions had small calcified foci (Figs. 1A, B). In spite of the antibiotic and antifungal therapies administered immediately after the admission because of suspected multiple brain abscesses that are typical of immunocompromised patients, the repeated postcontrast brain CT performed 14 days after the admission showed an increased size of the ring enhancing lesions. Multiple peripheral enhancing lesions surrounded by edema were

noted on the brain MR imaging performed 15 days after the admission. On the T2-weighted MR image, the central portion of some lesions showed low signal intensity due to the calcifications noted on CT. The majority of the lesions showed high signal intensity on the T1-weighted MR image, and this was possibly due to internal hemorrhage. The diffusion-weighted MR image (DWI) (b = 1,000 mm^2/s) revealed a decreased signal intensity change within the ring enhancing lesions (Figs. 1C–E). These findings of DWI ruled out the possible diagnosis of pyogenic or fungal abscess. The suspected diagnoses were HLH, metastasis or a toxoplasma abscess.

On 16th day from admission, the patient had craniotomy and biopsy of the left parietal lesion. The surgical findings revealed a red, grayish solid mass surrounding the peripheral yellowish fibrotic change. Histopathology showed a diffuse infiltration of CD3+ and CD8+ atypical lymphocytes (activated T-cell) and histiocytes in the parenchyma, and multifocal tissue necrosis. Epstein-Barr virus encoded RNA (EBER) was positive in many nuclei of these atypical lymphocytes. The histopathologic diagnosis was compatible with the EBV-infection hemophagocytic syndrome. Small foci of dystrophic calcifications were also noted. Perivascular infiltrations or meningeal infiltrations were not found (Fig. 1F). The patient underwent repeated immunosuppressive chemotherapy in accordance with the HLH-94 protocol, and the follow up brain MR imaging performed six months after the admission showed an improvement of the brain lesions, and an improvement of the symptoms was also noted.

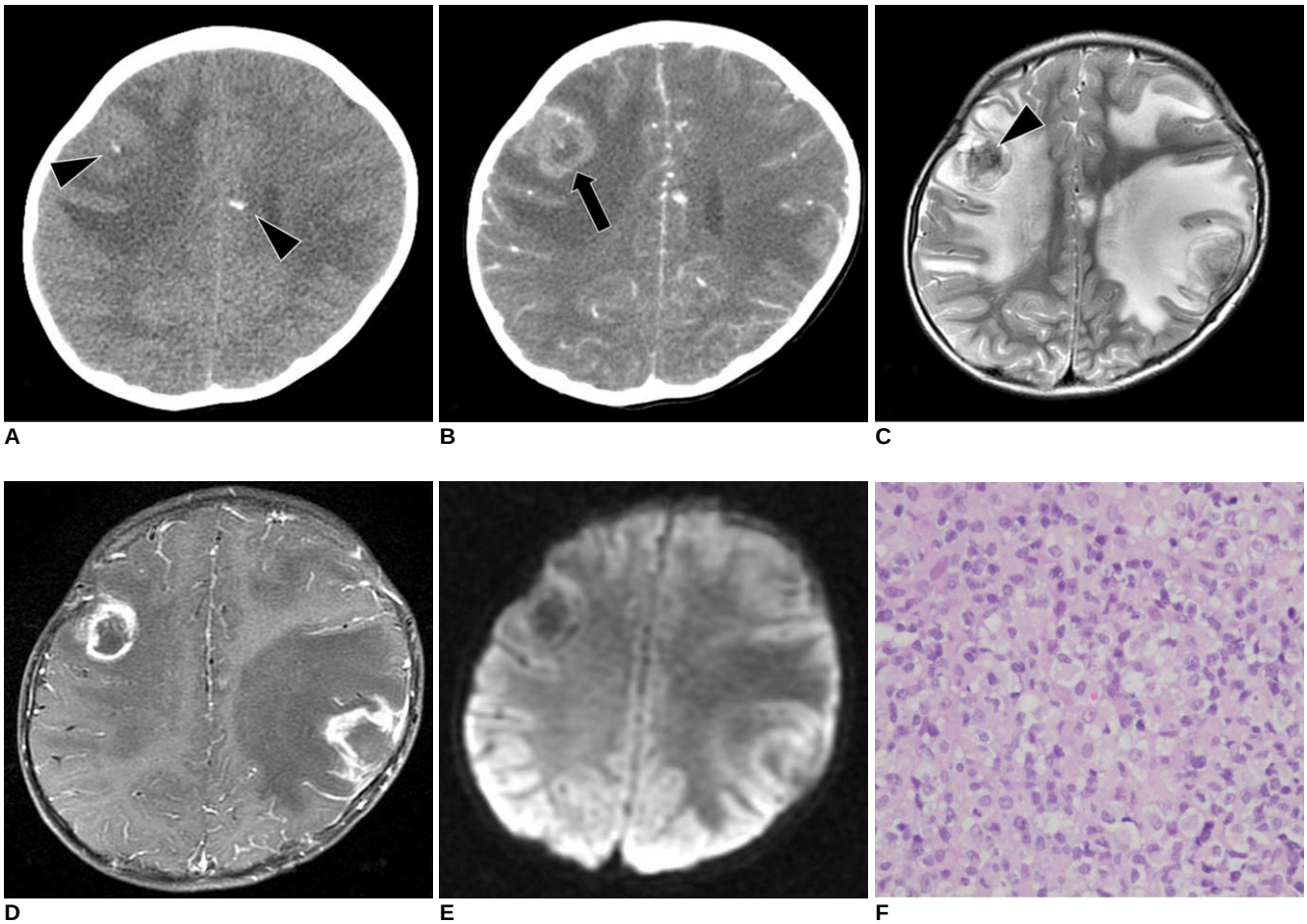

Fig. 1. A 3-year-old boy with the hemophagocytic syndrome and who presented seizures and fever.
A. On precontrast enhancement CT, several small parenchymal calcifications (arrowheads) can be seen in the subcortical area of both cerebral hemispheres.
B. Contrast-enhanced CT reveals several thick walled peripheral enhancing lesions (arrow) with surrounding perilesional edema. Focal internal calcifications were also noted.
C. The T2 weighted image reveals mixed signal intensity lesions with massive perilesional edema. The central, signal void portion of the right frontal mass shows calcification (arrowhead).
D. The contrast enhanced T1 weighted image reveals irregular, thick, ring enhancement.
E. No diffusion restriction in the lesions is noted on the diffusion weighted image.
F. Many foamy histiocytes and atypical lymphocytes infiltrations are observed (H & E stain; original magnification, ×400).

DISCUSSION

Hemophagocytic lymphohistiocytosis is a lethal disease characterized by the occurrence of hemophagocytic syndrome, and its course is divided into two distinct forms: the primary and the secondary HLH. The primary (familial) HLH exhibits an autosomal recessive mode of inheritance, and it usually occurs in infancy. The secondary HLH (as in our case) is associated with infection, malignancy and prolonged immunosuppression. However, both forms are characterized by similar symptoms and pathologic features (1, 2). The common symptoms of HLH are fever, hepatosplenomegaly, pancytopenia and skin rash (1). HLH may have a relapsing and remitting course, or it may rapidly progress to multiorgan failure and death. Approximately 30% of patients show neurological abnormalities such as seizures, alterations of the level of consciousness, hemiparesis, nuchal rigidity and ataxia (3). The CSF is normal in approximately 50% of cases. The CSF abnormalities are nonspecific, and they include increased levels of protein and low levels of glucose (4).

The histopathologic findings of HLH in pediatric patients with involvement of the CNS could be classified on the basis of the stages of the disease as determined microscopically, and the stages are characterized by increasing severity: stage I primarily shows only leptomeningeal infiltrates of lymphocytes and histiocytes/macrophages. stage II shows additional parenchymal involvement with perivascular infiltrations and stage III shows signs of cerebral tissue necrosis and demyelination in addition to the massive tissue infiltration that particularly affects the white matter (5). In our case, almost all the histopathologic findings, except the definite evidence of hemophagocytosis, were compatible with stage III of HLH.

The previously reported Imaging findings of HLH with CNS involvement are well correlated with those pathologic features (6–8). The reported CT findings are diffuse parenchymal atrophy, low attenuated lesions in the white matter and calcifications. Reduction of the volume leads to dilatation of the ventricular system and/or subdural fluid collections. The calcifications appear as gyriform linear areas that are more prominent in the regions of gray-white matter junctions. Some low attenuated parenchymal lesions show nodular or ring enhancement after contrast enhancement (7). The reported MR findings include diffuse leptomeningeal and perivascular enhancement, which corresponds to meningeal and perivascular infiltrations of histiocytes and lymphocytes, patchy areas of an increased T2 signal intensity in the white matter of the both cerebral hemispheres, and a diffuse parenchymal volume loss of the cerebrum and cerebellum. In some cases, nodular or ring enhancement of the parenchymal lesion appears due to the compromised blood-brain barrier that is associated with active demyelination. Our patient had similar findings, including nodular and irregular ring enhancing parenchymal lesions as well as calcifications in some lesions on CT and MRI (7, 8). DWI is useful for the differential diagnosis of ring enhancing lesions. The pyogenic or fungal brain abscesses have restricted diffusion at the center. However, necrotic brain tumors and toxoplasma abscesses do not exhibit restricted water diffusion (9, 10). It has been reported that diffusion restriction on DWI was noted in the white matter lesions of HLH (9). However, in our patient, the ring enhancing parenchymal lesions caused decreased signal intensity change at those centers on DWI. We postulate that the DWI features of this disease may vary with the lesion stage. During the early stage, the diffusion restriction of the white matter lesion may be associated with the neuronal loss along with cytotoxic edema and acute demyelination. During the later stage, the increased diffusion of the white matter lesion may be explained by tissue necrosis, which is similar to necrotic tumor (10). This DWI finding was well correlated with the pathologic findings in our case.

In conclusion, although the CT and MRI findings of HLH with ring enhancing parenchymal lesions are nonspecific and mimic abscess, and especially in the immunosuppressed patients, increased diffusion at the center on DWI may be a finding of HLH to differentiate it from abscess, which has restricted diffusion at the center. However, the pathologic correlation with DWI according to the lesion stage certainly needs further study with a larger number of patients.

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